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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/501,787 | 02/11/2000 | Laurent Coen | 03495.0187 | 4369 |

22852 7590 02/07/2003

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EXAMINER

BRANNOCK, MICHAEL T

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1646

DATE MAILED: 02/07/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.
09/501,787

Applicant(s)
Coen et al.

Examiner
Michael Brannock

Art Unit
1646



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED Dec 17, 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on Dec 17, 2002. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see NOTE below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE:

3. ☒ Applicant's reply has overcome the following rejection(s):
The rejection set forth in item 5 of Paper 13, 6/18/02, has been withdrawn

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
see Attachment to Advisory Action

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

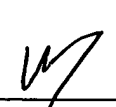
Claim(s) objected to: _____

Claim(s) rejected: 1-5, 8-11, 31, and 33-37

Claim(s) withdrawn from consideration: 12-30 and 32

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

10. ☐ Other: 

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Attachment to Advisory Action

1. Applicant is reminded that claims 1-5 and 8-11 are being examined only to the extent that the claims read on the in vivo delivery of a composition comprising fragment C of tetanus toxin plus at least 11 amino acids of fragment B. Further, claims 8-11, 31, 33-37 are being examined to the extent that they read on SMN protein, as set forth previously.

Information Disclosure Statement

2. As per item 4 of the previous Office action, Paper 13, 6/18/02, consideration of EP 0030496 has now been made of record, see the attached copy of PTO-1449.

Maintained Rejections

3. Claims 1-8, 11, 31, 34, 36 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as set forth previously in item 9 of Paper 13.

Applicant's arguments regarding the meaning and teaching of "in vivo retrograde transport" are unpersuasive. One of ordinary skill in the art appreciates that "retrograde" provides the direction of transport, i.e. away from an axon terminal toward the cell body, and that "transynaptic" refers to transport across a synapse. As set forth previously, one of ordinary skill in the art appreciates that the "in vivo retrograde transport" of TTC referred to in the 5780024

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patent includes both retrograde axonal transport and retrograde transsynaptic transport. This property of the TTC was old and widely known in the art at the time the 5780024 application was filed. At col 4, lines 37-42, U.S. Patent No: 5780024 teaches the following:

“By virtue of the TTC-mediated uptake by neurons, retrograde axonal transport within neurons, and retrograde transsynaptic transport between neurons, the SOD-1/TTC hybrid protein can be delivered from the peripheral nervous system into the CNS”.

Applicant's argues that U.S. Patent No: 5780024 does not demonstrate transsynaptic transport (i.e. transport between neurons). This argument has been fully considered but not deemed persuasive. As directly pointed to above, U.S. Patent No: 5780024 teaches retrograde transsynaptic transport, i.e., between neurons. The skilled artisan would have no reason to doubt this, and nor has any evidence been presented that it does not occur.

Applicant's arguments regarding the motivation to combine the teachings of U.S. Patent No: 5780024 and Fairweather have been substantial addressed previously. U.S. Patent 5780024 defines TTC moieties as those that contain the C-fragment plus additional amino acids comprising the B-fragment, so long as the function of the protein is not disrupted (see col 6, L31-56). The teachings of Fairweather provide evidence of the routine nature of adding to or subtracting residues from the C-fragment, and particularly adding residues from the B-fragment to the C-fragment as part of the ordinary optimization of operating parameters. In particular, the teachings of Fairweather provide a greater expectation of success when adding at least 11

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residues from the B-fragment, and also the motivation to do this, because the fragment is more easy to obtain in pure preparations (see col 2 of pg 2543).

Applicant argues that the pTet11 construct is missing 10 amino acids of the C fragment, and there is no evidence that such a construct retains activity. This argument has been fully considered but not deemed persuasive. Both Fairweather and U.S. Patent No: 5780024 indicate that it is routine to add or subtract residues from the C-fragment; in particular U.S. Patent No: 5780024 indicate that it is routine to delete residues from N-terminal of the C-fragment and to optimize with regard to activity (col 6, lines 63-65).

Applicant additionally challenges the idea that using a fragment that was more easily obtained would be desirable. This argument has been fully considered but not deemed persuasive. As indicated previously, Fairweather provide evidence as to the routine nature of optimizing operation parameters with regard to the design and use of TCC. Fairweather is not being relied on to teach the applicability of using a TCC for the introduction of a foreign protein into the CNS, this teaching is provided by U.S. Patent No: 5780024. Both Fairweather and U.S. Patent No: 5780024 indicate that it is routine to add or subtract residues from the C-fragment. Applicant's arguments regarding a distinction between "convenience" and "optimization" are unpersuasive. An artisan of ordinary skill would understand from the language used in col 6 of U.S. Patent No: 5780024 that the patent discloses that residues can be added, and that this can be done simply, but not exclusively, as a matter of convenience. Additionally, an artisan,

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particularly one of ordinary skill, would recognize that optimization of convenience is, itself, part of the routine optimization of operating parameters.

Applicant challenges the examiner's assertion that the citation of a reference published by the Fairweather laboratory would provide motivation to use a construct from a different reference, albeit from the same laboratory, as a source of material for practicing the invention. This argument is persuasive, however that was not the examiner's intention, the examiner merely pointed out that the skilled artisan would be made aware of work in the Fairweather laboratory by the 5780024 patent, but it is the description of the TCC moiety at col 6 of the 5780024 patent that would lead the artisan to the Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987 reference.

Applicant's arguments regarding SEQ ID NO: 16 and the decision in *UW v. Eli Lilly*, 2002 WL 1305996, *17 (Bd. Pat. Applicant argues that. & Interf.) are unpersuasive. The instant specification puts forth that SEQ ID NO: 16 is the sequence of C-fragment plus 11 residues from the B-fragment (pg 19). The 5780024 patent provides an example of the C-fragment plus 9 residues of the B-fragment (col 6, L50-52). 5780024 provides the teaching and suggestion that more or less of the B-fragment can be retained on the C-fragment. Thus it would be obvious to the artisan to chose the 10th, 11th, 12th, ect. residue of the B-fragment (the exact sequence of which is known) as part of the routine optimization of operating parameters. The fact pattern in *UW v. Eli Lilly* is completely unrelated to the instant case. As to the matter of *UW v. Eli Lilly*, the artisan would be required to randomly pick from an astronomical number of possible

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nucleotide changes to arrive at the sequence disclosed by UW based on knowledge of the sequence disclosed by Lilly. This would be a practical impossibility, thus the two sequences are patentably distinct.

4. Claims 9 and 10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to claims 1-8, 11 and 31, above, and in further view of Fishman et al., J. Neurological Sciences 98(311-325)1990, as set forth previously.

Applicant's arguments have been substantially addressed above.

5. Claims 1-8, 11, 31, 33-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948, as set forth previously. Applicant's arguments have been substantially addressed above.

6. Claims 1-8, 11, 31, 34 and 36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995, in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as set forth previously in item 13 of Paper 13.

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Applicant's arguments regarding the alleged lack of a demonstration of transynaptic transport are unpersuasive. Francis et al. provide the specific suggestion that the hybrid protein could be used to enter the CNS through retrograde trans-synaptic transport, as has been pointed to by Applicant at page 14 of the response.

Applicant relies on previous arguments regarding the motivation to combine Francis et al. (inventors of the 5780024 patent) and Fairweather. These arguments have been substantially addressed previously. The examiner maintains that the teachings of Fairweather provide evidence of the routine nature of adding to or subtracting residues from the C-fragment, and particularly adding residues from the B-fragment (the sequence of which is well known), as part of the ordinary optimization of operating parameters. In particular, the teachings of Fairweather provide a greater expectation of success when adding at least 11 residues from the B-fragment, and also the motivation to do this, because the fragment is more easy to obtain in pure preparations (see col 2 of pg 2543).

7. Claims 9 and 10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to claims 1-8, 11 and 31, above, and in further view of Fishman et al., J. Neurological Sciences 98(311-325)1990, as set forth previously in item 14 of Paper 13.

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Applicant's arguments have been addressed previously. As with Francis et al., Applicant asserts that Fishman provide only speculation regarding transynaptic. This argument has been fully considered but not deemed persuasive. Again, Fishman provide further evidence as to the fact that transynaptic retrograde transport would be expected of such constructs, see page 323, middle paragraph of Fishman et al..

8. Claims 6-8, 11, 31, 33, 35, 36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948, as set forth previously in item 15 of Paper 13. Applicant's arguments have been addressed previously.

9. Claims 6-8, 11, 31, 33-36 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to 6-8 , above, and in further view of Liston et al., Nature 379(6563)349-53, as set forth previously in item 16 of Paper 13. Applicant's arguments have been addressed previously.

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Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

January 29, 2003


YVONNE EYLER, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1000